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ORIGINAL ARTICLE

Novel thiosemicarbazone derivatives containing benzimidazole moiety: Green synthesis and anti-malarial activity

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Abstract A series of (*E*)-2-[5-chloro-1-(1*H*-benzo[d]imidazol-2-yl)ethylidene] N-(substituted) hydrazine carbothioamide (**7a**–**7t**) and (*E*)-2-[1-(1*H*-benzo[d]imidazol-2-yl)ethylidene] N-(substituted) hydrazine carbothioamide (**8a**–**8t**) were prepared via the synthesis of 1-(substituted-1*H*-benzimidazol-2-yl) ethanol (**3a**–**3b**) which was synthesized by the condensation of substituted o-phenylenediamine (**2a**–**2b**) with DL-lactic acid (**1**) followed by oxidation with sodium hypochlorite in mild acidic condition to form the corresponding ketones **4a**–**4b**. Final compounds were formed by condensation of **4a**–**4b** with different thiosemicarbazides **6a**–**6t**. A total of 40 compounds were synthesized and characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, Mass spectral technique and elemental analysis, in addition they were evaluated for anti-malarial properties. Among the compounds tested **7o**, **7p**, **7q**, **7r**, **7s**, **8e** and **8h** exhibited good antimalarial activity *in vitro*.

1. Introduction

Malaria is endemic in over 100 countries, affecting especially tropical areas of Africa, Asia and Latin America. It is responsible for high mortality and morbidity in these regions, being especially lethal to children and pregnant women. (De Oliveira et al., 2008) According to World Health Organization up to one million people die of malaria worldwide, every year (WHO, Geneva, 2006). Human malaria is caused by four different species of *Plasmodium*: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae*. The most severe form is caused by *P. falciparum*, which leads to the death of about 1% of infected patients. Although the use of drugs has effectively resulted in successful treatment of Plasmodium infections, drug resistances in Plasmodium have been reported (Bloland, 2001; Gogtay et al., 2006; Kshirsagar, 2006). Owing to growing resistance, the development of potent antimalarials is recommended to fulfil this challenge. Recently there have been a lot of studies using iron-chelating agents as a possible treatment for malaria (Cabantchik, 1994; Kontoghiorghes et al., 2010). Thiosemicarbazones are known iron-chelating agents by bonding through the sulphur and

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azomethine nitrogen atoms (Walcourt et al., 2004). Their activity against extracellular protozoan such as *P. falciparum*, *Trichomonas vaginalis*, *Trypanosoma cruzi*, and other parasites was demonstrated by several researchers (Bharti et al., 2002; Greenbaum et al., 2004).

On the other hand, the structural similarities between benzimidazole nucleus and various biological compounds such as purine base of the DNA and its presence in vitamin B_{12} have made it important in the pharmaceutical industry. As a result of this, benzimidazoles have been termed as key structures for drug design (Panda et al., 2012). Thus, because of its increasing medicinal importance, great efforts have been made to develop an efficient and economical method for the synthesis of its large number of new derivatives. This inspired us to study the biological activities of thiosemicarbazone analogues of benzimidazole. In this research article, we have reported the synthesis of new benzimidazole-thiosemicarbazone derivatives. These compounds were tested for *in vitro* antimalarial screening.

2. Materials and methods

2.1. Chemistry

Melting points were determined on a Büchi 535 melting point apparatus and are uncorrected. A CEM Discover microwave synthesizer (Model No. 908010) operating at 180/264 V and 50/60 Hz with a microwave power maximum level of 700 W and microwave frequency of 2455 MHz was employed for microwave-assisted experiments done in this work. Infrared spectra were recorded on a Perkin-Elmer 841 using samples in potassium bromide discs. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer using DMSO-d_6 as a solvent and TMS as an internal standard. Mass spectra were recorded on a TSQ-Quantum Access Mass spectrometer by ESI (electron spray ionization) method. Elemental analyses were performed on a Micro Variant CHN elemental analyser. TLC was performed on a Merck DC Alufolien with Kieselgel 60F_{254} from Merck Co., Germany. All the raw-materials were purchased from Sigma–Aldrich Co, Germany.

2.1.1. Synthesis of 1-(5-Chloro-1H-benzimidazol-2-yl) ethanol (**3a**) (Patel et al., 2013)

In a 50 mL glass round bottomed flask, 4-Chlorobenzene-1,2-diamine (**2a**) (0.003 mmol) and D,L-lactic acid (**1**) (88% approx.) (8 mL) were mixed. To this mixture, ethylene glycol (5 mL) was added. The reaction mixture was heated by an open vessel method in the Discover Microwave Synthesizer (CEM Matthews Inc., USA) at 300 W with total irradiation time of 35 min. On cooling, the reaction mixture was treated with a saturated solution of $NaHCO_3$. (pH 8). After neutralization, the residue obtained was dissolved in methanol and filtered. The filtrate was concentrated to dryness. The residue was then collected by filtration as a yellow solid form. The yield was 78% and product was further used after crystallization from alcohol, m.p. was taken at 168–170 °C. Reaction progress was checked by TLC plates using ethyl acetate: toluene (4:1) as the mobile phase. IR (KBr): 3360 (NH), 3077 (C–H benzene), 1599 (C═C & C═N), 1113 (C–O)cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.49–1.51 (d, 3H, J = 8 Hz,CH_3), 4.68–4.75 (m, 1H, CH), 5.77–5.79 (d, 1H, J = 8 Hz, OH), 7.14–7.16 (d, 1H, J = 8 Hz, Ar-H), 7.80–7.82 (d, 1H, J = 7.9 Hz, Ar-H), 8.38–8.41 (d, 1H, J = 8.9 Hz, Ar-H), 13.05 (s, 1H, NH). HRMS (m/z, ESI): M$^+$ 196.05, [M + 2] 198.05. Anal. Calcd. for $C_9H_9ClN_2O$ (Mol. Wt. 196.63): C, 54.97; H, 4.61; N, 14.25. Found: C, 54.94; H, 4.58; N, 14.23.%.

2.1.1.1. Synthesis of 1-(1H-benzimidazol-2-yl) ethanol (**3b**).

Similarly, we have synthesized compound (**3b**) by taking compound (**2b**) as a starting material. The product was isolated as a light yellow solid with 75% yield and m.p. was taken at 165–167 °C. IR (KBr): 3420 (NH), 3107 (C–H benzene), 1492 (C═C & C═N), 1125 (C–O)cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.56–1.58 (d, 3H, J = 8 Hz, CH_3), 4.75–4.84 (m, 1H, CH), 5.68–5.70 (d, 1H, J = 8 Hz, OH), 7.25–7.27 (d, 1H, J = 8 Hz, Ar-H), 7.35–7.40 (t, 1H, J = 7.5 Hz, Ar-H), 8.52–8.54 (d, 1H, J = 8 Hz, Ar-H), 12.96 (s, 1H, NH). HRMS (m/z, ESI): M$^+$ 162.10, [M + 1] 163.10. Anal. Calcd. for $C_9H_{10}N_2O$ (Mol. Wt. 162.19): C, 66.65; H, 6.21; N, 17.27. Found: C, 66.62; H, 6.18; N, 17.25.%.

2.1.2. Synthesis of 1-(5-chloro-1H-benzimidazol-2-yl) ethanone (**4a**)

To a solution of 1-(5-chloro-1*H*-benzimidazol-2-yl) ethanol (**3a**) (0.001 mmol) in glacial acetic acid (10 mL) was added gradually a solution of 4% sodium hypochlorite solution (NaOCl) (0.0013 mmol/25 mL) in an ice bath because of the exothermic reaction. After addition of NaOCl, the reaction mixture was stirred for 20 min at room temperature. It was necessary to stir the mixture vigorously as the reaction mixture was two-phased. The reaction mixture was then tested for excess hypochlorite with starch-iodide paper. The addition of 0.5 mL of a saturated sodium bisulphite (Na_2SO_3) solution was done to remove the blue-black color. The mixture was swirled after addition and then tested again until the complete removal of hypochlorite. After that the reaction was neutralized with the help of 6 M NaOH. The product was then obtained via the extraction process. In a separating funnel, product was extracted with 3 × 5 mL portions of methylene dichloride (CH_2Cl_2). An aqueous layer was removed and the combined organic layer was dried with Na_2SO_4 for about 5–10 min with occasional stirring and then sodium sulphate was isolated with Buchner funnel. The remaining organic extract was taken in a rotary evaporator to remove the solvent under reduced pressure. The yellow precipitates were collected in 75% yield and dried further. The product started decomposing before reaching its M.P. The reaction progress was checked by TLC using Ethyl acetate: Toluene (4:1) as solvents; IR (KBr): 3368 (NH), 3060 (C–H benzene), 1699 (C═O) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.70 (s, 3H, CH_3), 7.35–7.39 (d, 1H, J = 8 Hz, Ar-H), 7.78–7.80 (d, 1H, J = 8 Hz, Ar-H), 8.24 (s, 1H, Ar-H), 13.5 (s, 1H, NH). HRMS (m/z, ESI): M$^+$ 194.02, [M + 2] 196.05. Anal. Calcd. for $C_9H_7ClN_2O$ (Mol. Wt. 194.62): C, 55.54; H, 3.63; N, 14.39. Found: C, 55.50; H, 3.60; N, 14.36.%.

2.1.2.1. Synthesis of 1-(1H-benzimidazol-2-yl) ethanone (**4b**).

Similarly, 1-(1*H*-benzimidazol-2-yl) ethanone (**4b**) was synthesized by taking 1-(1*H*-benzimidazol-2-yl) ethanol (**3b**) as a starting material. The yellow precipitates were obtained in 76% yield. The product started decomposing before reaching its M.P. IR (KBr): 3375 (N–H), 3054 (C–H benzene), 1685 (C═O) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.48 (s, 3H,

CH_3), 7.28–7.30 (d, 1H, J = 8 Hz, Ar-H), 7.68–7.70 (d, J = 8 Hz, Ar-H), 8.50 (s, 1H, Ar-H), 13.28 (s, 1H, NH). HRMS (m/z, ESI): M^+ 160.06, [M + 1] 161.07. Anal. Calcd. for $C_9H_8N_2O$ (Mol. Wt. 160.17): C, 67.49; H, 5.03; N, 17.49. Found: C, 67.46; H, 5.00; N, 17.47.%.

*2.1.3. General procedure for the synthesis of N^4-alkyl and aryl thiosemicarbazides (**6a–6t**)*

The alkyl or aryl isothiocyanate (0.001 mmol) was added dropwise in a solution of hydrazine (0.001 mmol) in methanol (6 mL). The reaction was irradiated by microwaves in a Discover Microwave Synthesizer (CEM Matthews Inc., USA) at 180 W with a total irradiation time of 3–5 min. The excess solvent was then removed by evaporation *in vacuo* and the crude product was dissolved in chloroform (5 mL) and this solution was added into multifold volume of petroleum ether (40–60 °C) at constant stirring. The precipitates obtained were used directly for the next step. All thiosemicarbazides (**6a–6t**) were obtained by the general method described above.

*2.1.4. General procedure illustrating the synthesis of (E)-2-[1-(5-chloro-1H-benzo[d]imidazol-2-yl)ethylidene] N-hydrazine carbothioamide (**7a–7t**)*

An alkyl or aryl thiosemicarbazide (**6a–6t**) (0.001 mmol) and 10 drops of glacial acetic acid were added to a solution of 1-(5-chloro-1*H*-benzimidazol-2-yl) ethanone (**4a**) in methanol (6 mL). The reaction mass was heated in a Discover Microwave Synthesizer (CEM Matthews Inc., USA) at 180 W with a total irradiation time of 25–35 min. The product was obtained upon cooling, and then dried. The reaction progress was checked by TLC taking Ethyl acetate: Toluene (4:1) as the mobile phase. The product was re-crystallized by 95% ethanol. The product was obtained as a brown colored solid in good yield which was further characterized by FT-IR, ^{1}H NMR, Mass spectra and elemental analysis. A series of all compounds (**7a–7t**) were synthesized by the above described method.

*2.1.4.1. (E)-2-(1-[5-Chloro-1H-benzo[d]imidazol-2-yl)ethylidene] hydrazine carbothioamide (**7a**) (Patel et al., 2013).* The reaction mass was heated in MW at 180 W with a total irradiation time of 25 min. The product was a light brown solid; 75% yield; m.p. 214–215 °C; IR (cm^{-1}, KBr): 3454 (–NH), 1213 (C═S), 1531 (C═N), 1584 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.38 (s, 3H, –CH_3), 7.07–7.55 (m, 1H, Ar-H), 7.67–7.65 (d, 1H, J = 7.6 Hz, Ar-H), 7.92 (s, 1H, Ar-H), 8.57 (s, 2H, –NH_2), 10.73 (s, 1H, –NH), 12.88 (s, 1H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6) Benzimidazole C: [152.65 (C), 140.48 (C), 138.89 (C), 130.07 (C–Cl), 126.56 (CH), 117.29 (CH), 116.34 (CH)], 180.34 (C═S), 157.60 (N═CH), 25.46 (CH_3); HRMS (m/z, ESI): M^+ 267.03, [M + 2] 269.03. Anal. Calcd. for $C_{10}H_{10}ClN_5S$ (Mol. Wt. 267.73): C, 44.86; H, 3.76; N, 26.12. Found: C, 44.84; H, 3.73; N, 26.10%.

*2.1.4.2. (E)-2-[1-(5-Chloro-1H-benzo[d]imidazol-2-yl)ethylidene] N-phenylhydrazine carbothioamide (**7b**) (Patel et al., 2013).* The reaction mass was heated in MW at 180 W with a total irradiation time of 35 min. The product was a light brown solid; 85% yield; m.p. at 161–162 °C; IR (cm^{-1}, KBr): 3205 (NH), 1189 (C═S), 1514 (C═N), 1596 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.48 (s, 3H, CH_3), 7.24–7.26 (d, 1H, J = 8 Hz, Ar-H), 7.40–7.44 (t, 1H, J = 7.9 Hz, Ar-H), 7.49–7.51 (d, 1H, J = 8 Hz, Ar-H), 7.59–7.64 (d, 1H, J = 7.6 Hz, Ar-H), 8.36 (s, 1H, Ar-H), 10.40 (s, 1H, NH), 11.07 (s, 1H, NH), 13.02 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) Benzimidazole C: [152.45 (C), 140.28 (C), 137.39 (C), 130.17 (C–Cl), 126.78 (CH), 117.56 (CH), 116.49 (CH)], Arom-C: [140.33 (C), 127.58 (CH), 128.44 (C), 129.26 (CH), 184.34 (C═S), 156.58 (N═CH), 25.50 (CH_3); HRMS (m/z, ESI): M^+ 342.9, [M + 2] 344.9. Anal. Calcd. for $C_{16}H_{14}ClN_5S$ (Mol. Wt. 343.83): C, 55.89; H, 4.10; N, 20.37. Found: C, 55.87; H, 4.06; N, 20.33%.

*2.1.4.3. (E)-2-[1-(5-Chloro-1H-benzo[d]imidazol-2-yl)ethylidene] N-ethylhydrazine carbothioamide (**7c**) (Patel et al., 2013).* The reaction mass was heated in MW at 180 W with a total irradiation time of 25 min. The product was a light Brown solid; 83% yield; m.p. 223–224 °C; IR (cm^{-1}, KBr): 3435 (NH), 1199 (C═S), 1492 (C═N), 1549 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.38–2.46 (s, 3H, CH_3), 1.16–1.20 (t, 3H, J = 6.8 Hz, CH_2), 3.66–3.68 (t, 2H, J = 6.8 Hz, CH_3), 7.24 (d, 1H, J = 7.5 Hz, Ar-H), 7.55 (d, 1H, J = 7.5 Hz, Ar-H), 7.70 (s, 1H, Ar-H), 8.96 (s, 1H, NH), 10.68 (s, 1H, NH), 12.82 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) Benzimidazole C: [152.25 (C), 139.98 (C), 137.86 (C), 130.53 (C–Cl), 126.95 (CH), 117.87 (CH), 116.93 (CH)], 180.15 (C═S), 156.45 (N═CH), 42.50 (CH_2), 25.48(CH_3), 28.56 (CH_3); HRMS (m/z, ESI): M^+ 296.10, [M + 2] 298.10. Anal. Calcd. for $C_{12}H_{14}ClN_5S$ (Mol. Wt. 295.79): C, 48.73; H, 4.77; N, 23.68. Found: C, 48.71; H, 4.75; N, 23.65.%.

*2.1.4.4. (E)-2-[1-(5-Chloro-1H-benzo[d]imidazol-2-yl)ethylidene] N-(n-butyl) hydrazine carbothioamide (**7d**) (Patel et al., 2013).* The reaction mass was heated in MW at 180 W with a total irradiation time of 25 min. The product was a brown solid; 69% yield; m.p. 203–204 °C; IR (cm^{-1}, KBr): 3448 (NH), 1216 (C═S), 1419 (C═N), 1541 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.88–0.91 (t, 3H, J = 6.8 Hz, CH_3), 1.30–1.35 (m, 2H, CH_2), 1.57–1.87 (m, 2H, CH_2), 2.40–2.42 (t, 1H, J = 7.9 Hz, CH_2), 3.62 (s, 2H, CH_3), 7.27–7.28 (d, 1H, J = 7.5 Hz, Ar-H), 7.55 (d, 1H, J = 7.8 Hz, Ar-H), 7.71 (s, 1H, Ar-H), 8.94 (s, 1H, NH), 10.68 (s, 1H, NH), 12.83 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) Benzimidazole C: [152.30 (C), 140.25 (C), 137.97 (C), 130.32 (C–Cl), 126.92 (CH), 117.85 (CH), 116.96 (CH)], 179.45 (C═S), 156.66 (N═CH), Butyl C: [48.76 (CH_2), 42.59 (CH_2), 31.48(CH_2)], 25.56 (CH_3); HRMS (m/z, ESI): M^+ 323.04, [M + 2] 325.04. Anal. Calcd. for $C_{14}H_{18}ClN_5S$ (Mol. Wt. 323.84): C, 51.92; H, 5.60; N, 21.63. Found: C, 51.90; H, 5.58; N, 21.61%.

*2.1.4.5. (E)-2-[1-(5-Chloro-1H-benzo[d]imidazol-2-yl)ethylidene] N-cyclohexyl hydrazine carbothioamide (**7e**) (Patel et al., 2013).* The reaction mass was heated in MW at 180 W with a total irradiation time of 25 min. The product was a brown solid; 85% yield; m.p. 215–216 °C; IR (cm^{-1}, KBr): 3420 (NH), 1206 (C═S), 1519 (C═N), 1594 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6):δ 1.22–1.89 (m, 11H, Cyclohex-H), 2.40–2.46 (s, 3H, CH_3), 7.28–7.31 (d, 1H, J = 7.9 Hz, Ar-H), 7.51–7.53 (d, 1H, J = 8 Hz, Ar-H), 7.71–7.77 (s, 1H, Ar-H), 9.80 (s, 1H, NH), 10.55 (s, 1H, NH), 13.10 (s,

1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [152.36 (C), 140.28 (C), 137.98 (C), 130.38 (C–Cl), 126.96 (CH), 117.75 (CH), 116.87 (CH)], 179.15 (C═S), 156.68 (N═CH), Cyclohexyl C: [60.05 (CH), 42.15 (CH_2), 35.19 (CH_2), 35.05 (CH_2)], 25.66 (CH_3); HRMS (*m*/*z*, ESI): M^+ 349.11, [M + 2] 351.11. Anal. Calcd. for $C_{16}H_{20}ClN_5S$ (Mol. Wt. 349.88): C, 54.92; H, 5.76; N, 20.02. Found: C, 54.90; H, 5.74; N, 20.00%.

*2.1.4.6. (E)-2-[1-(5-Chloro-1H-benzo[d]imidazol-2-yl)ethylidene] N-(4-chlorophenyl) hydrazine carbothioamide (**7f**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 30 min. The product was a brown solid; 77% yield; m.p. 178–180 °C; IR (cm^{-1}, KBr): 3375 (NH), 1215 (C═S), 1560 (C═N), 1620 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6):δ 2.50 (s, 3H, CH_3), 7.26–7.28 (d, 1H, *J* = 8 Hz, Ar-H), 7.33–7.35 (d, 1H, *J* = 8 Hz, Ar-H), 7.53–7.55 (d, 1H, *J* = 8 Hz, Ar-H), 7.59–7.61 (d, 1H, *J* = 8.5 Hz, Ar-H), 7.75–7.77 (d, 1H, *J* = 8 Hz, Ar-H), 7.89 (s, 1H, Ar-H), 10.46 (s, 1H, NH), 11.25 (s, 1H, NH), 13.15 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [152.34 (C), 140.42 (C), 137.60 (C), 130.30 (C–Cl), 126.52 (CH), 117.32 (CH), 116.34 (CH)], 184.36 (C═S), 157.22 (N═CH), Arom-C: [144.48 (C), 142.54 (C–Cl), 128.78 (CH, CH), 127.88 (CH,CH)], 25.54 (CH_3); HRMS (*m*/*z*, ESI): M^+ 378.03, [M + 2] 380.03. Anal. Calcd. for $C_{16}H_{13}Cl_2N_5S$ (Mol. Wt. 378.28): C, 50.80; H, 3.46; N, 18.51. Found: C, 50.00; H, 3.43; N, 18.43%.

*2.1.4.7. (E)-2-[1-(5-Chloro-1H-benzo[d]imidazol-2-yl)ethylidene] N-(4-nitrophenyl) hydrazine carbothioamide (**7g**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 35 min. The product was a brown solid; 75% yield; m.p. 205–208 °C; IR (cm^{-1}, KBr): 3320 (NH), 1195 (C═S), 1525 (C═N), 1605 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.68 (s, 3H, CH_3), 7.39–7.41 (d, 1H, *J* = 8 Hz, Ar-H), 7.72–7.74 (d, 1H, *J* = 8 Hz, Ar-H), 7.84–7.86 (d, 1H, *J* = 8 Hz, Ar-H), 8.04–8.06 (d, 1H, *J* = 8 Hz, Ar-H), 8.20 (s, 1H, Ar-H), 9.62 (s, 1H, NH), 10.77 (s, 1H, NH), 13.07 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [152.26 (C), 140.38 (C), 137.58 (C), 130.28 (C–Cl), 126.44 (CH), 117.25 (CH), 116.27 (CH)], 184.25 (C═S), 157.08 (N═CH), Arom-C: [144.60 (C), 125.16 (CH, CH), 125.78 (CH, CH), 143.94 (C–NO_2)], 25.56 (CH_3); HRMS (*m*/*z*, ESI): M^+ 388.03, [M + 2] 390.03. Anal. Calcd. for $C_{16}H_{13}ClN_6O_2S$ (Mol. Wt. 388.83): C, 49.42; H, 3.37; N, 21.61. Found: C, 49.38; H, 3.33; N, 21.58%.

*2.1.4.8. (E)-2-[1-(5-Chloro-1H-benzo[d]imidazol-2-yl)ethylidene] N-(4-methoxyphenyl) hydrazine carbothioamide (**7h**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 30 min. The product was a brown solid; 75% yield; m.p. 192–194 °C; IR (cm^{-1}, KBr): 3350 (NH), 1215 (C═S), 1570 (C═N), 1630 (C═C), 1274 (C–O–C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.51 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 6.86–6.88 (d, 1H, *J* = 8 Hz, Ar-H), 7.26–7.28 (d, 1H, *J* = 8 Hz, Ar-H), 7.33–7.35 (d, 1H, *J* = 8 Hz, Ar-H), 7.73–7.76 (d, 1H, *J* = 8 Hz, Ar-H), 7.82 (s, 1H, Ar-H), 10.38 (s, 1H, NH), 11.07 (s, 1H, NH), 13.15 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [152.28 (C), 140.41 (C), 137.62 (C), 130.30 (C–Cl), 126.48 (CH), 117.28 (CH), 116.30 (CH)], 184.28 (C═S), 157.18 (N═CH), Arom-C: [160.10 (C), 132.48 (C), 127.96 (CH, CH), 114.85 (CH, CH)], 59.25 (OCH_3), 25.56 (CH_3); HRMS (*m*/*z*, ESI): M^+ 373.12, [M + 2] 375.12. Anal. Calcd. for $C_{17}H_{16}ClON_5S$ (Mol. Wt. 373. 85): C, 54.61; H, 4.31; N, 18.73. Found: C, 50.43; H, 4.29; N, 18.71%.

*2.1.4.9. (E)-2-[1-(5-Chloro-1H-benzo[d]imidazol-2-yl)ethylidene] N-(isopropyl) hydrazine carbothioamide (**7i**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 25 min. The product was a brown solid; 72% yield; m.p. 220–222 °C; IR (cm^{-1}, KBr): 3373 (NH), 2974(C(CH_3)), 1220 (C═S), 1580 (C═N), 1620 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.27–1.29 (d, 6H, *J* = 8 Hz,(CH_3)$_2$), 2.56 (s, 3H, CH_3), 4.25–4.30 (m, 1H, CH), 7.12–7.14 (d, 1H, *J* = 8 Hz, Ar-H), 7.38–7.40 (d, 1H, *J* = 8 Hz, Ar-H), 7.82 (s, 1H, Ar-H), 10.55 (s, 1H, NH), 11.17 (s, 1H, NH), 13.25 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [152.44 (C), 140.48 (C), 137.70 (C), 130.56 (C–Cl), 126.52 (CH), 117.34 (CH), 116.47 (CH)], 178.58 (C═S), 157.35 (N═CH), Isopropyl C: [52.10 (CH), 33.24 (CH_3, CH_3)], 25.35 (CH_3); HRMS (*m*/*z*, ESI): M^+ 309.11, [M + 2] 311.11. Anal. Calcd. for $C_{13}H_{16}ClN_5S$ (Mol. Wt. 309.81): C, 50.40; H, 5.21; N, 22.60. Found: C, 50.37; H, 5.19; N, 22.57%.

*2.1.4.10. (E)-2-[1-(5-Chloro-1H-benzo[d]imidazol-2-yl)ethylidene] N-(tert-butyl) hydrazine carbothioamide (**7j**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 25 min. The product was a brown solid; 85% yield; m.p. 211–214 °C; IR (cm^{-1}, KBr): 3298 (NH), 1235 (C═S), 1565 (C═N), 1593 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.52–1.68 (m, 9H, (CH_3)$_3$), 2.64 (s, 3H, CH_3), 7.08–7.10 (d, 1H, *J* = 8 Hz, Ar-H), 7.28–7.31 (d, 1H, *J* = 7.9 Hz, Ar-H), 7.74 (s, 1H, Ar-H), 9.46 (s, 1H, NH), 12.77 (s, 1H, NH), 13.53 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [152.45 (C), 140.48 (C), 137.76 (C), 130.66 (C–Cl), 126.58(CH), 117.58 (CH), 116.67 (CH)], 178.38 (C═S), 157.55 (N═CH), t-butyl C: [62.36 (C), 40.26 (CH_3, CH_3, CH_3)], 25.30 (CH_3); HRMS (*m*/*z*, ESI): M^+ 323.15, [M + 2] 325.15. Anal. Calcd. for $C_{14}H_{18}ClN_5S$ (Mol. Wt. 323.84): C, 51.92; H, 5.60; N, 21.63. Found: C, 51.89; H, 5.58; N, 21.60%.

*2.1.4.11. (E)-2-[1-(5-Chloro-1H-benzo[d]imidazol-2-yl)ethylidene] N-(benzyl) hydrazine carbothioamide (**7k**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 35 min. The product was a brown solid; 65% yield; m.p. 218–219 °C; IR (cm^{-1}, KBr): 3379 (NH), 1236 (C═S), 1546 (C═N), 1583 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.51 (s, 3H, CH_3), 4.72 (s, 2H, CH_2), 7.23–7.75 (m, 5H, Ar-H), 8.31 (s, 1H, Ar-H), 9.70 (s, 1H, NH), 11.03 (s, 1H, NH), 13.13 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [152.48 (C), 140.52 (C), 137.78 (C), 130.60 (C–Cl), 126.58(CH), 117.57 (CH), 116.69 (CH)], 178.45 (C═S), 157.58 (N═CH), Arom-C: [138.72 (C), 129.95 (CH, CH), 127.30 (CH, CH), 126.98 (C)], 55.34 (CH_2), 25.25 (CH_3); HRMS (*m*/*z*, ESI): M^+

357.26, [M + 2] 359.26. Anal. Calcd. for $C_{17}H_{16}ClN_5S$ (Mol. Wt. 357.86): C, 57.06; H, 4.51; N, 19.57. Found: C, 57.00; H, 4.48; N, 19.55%.

*2.1.4.12. (E)-2-[1-(5-Chloro-1H-benzo[d]imidazol-2-yl)ethylidene] N-(2,4-dichlorophenyl) hydrazine carbothioamide (**7l**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 30 min. The product was a brown solid; 68% yield; m.p. 180–182 °C; IR (cm^{-1}, KBr): 3375 (NH), 1242 (C═S), 1543 (C═N), 1581 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.50 (s, 3H, CH_3), 7.27 (d, 1H, J = 8.5 Hz, Ar-H), 7.40–7.44 (d, 1H, J = 8.5 Hz, Ar-H), 7.66–7.68 (d, 1H, J = 7.9 Hz, Ar-H), 7.88–7.90 (d, 1H, J = 7.9 Hz, Ar-H), 8.37 (s, 1H, Ar-H), 8.42 (s, 1H, NH), 9.85 (s, 1H, NH), 10.68 (s, 1H, NH), 13.09 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [152.42 (C), 140.48 (C), 137.75 (C), 130.58 (C–Cl), 126.63(CH), 117.62 (CH), 116.74 (CH)], 185.28 (C═S), 157.63 (N═CH), Arom-C: [135.60 (C), 134.23 (C–Cl), 133.86 (CH), 133.18 (C–Cl), 132.54 (CH), 125.58 (CH)], 25.32 (CH_3); HRMS (*m*/*z*, ESI): M^+ 412.28, [M + 2] 414.28. Anal. Calcd. for $C_{16}H_{12}Cl_3N_5S$ (Mol. Wt. 412.72): C, 46.56; H, 2.93; N, 16.97. Found: C, 46.54; H, 2.90; N, 16.95%.

*2.1.4.13. (E)-2-[1-(5-Chloro-1H-benzo[d]imidazol-2-yl)ethylidene] N-(2-methoxyphenyl) hydrazine carbothioamide (**7m**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 30 min. The product was a brown solid; 72% yield; m.p. 192–193 °C; IR (cm^{-1}, KBr): 3312 (NH), 1204 (C═S), 1597 (C═N), 1620 (C═C), 1274 (C–O–C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.50 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 6.90–7.26 (m, 4H, Ar-H), 7.42–7.50 (t, 1H, J = 8 Hz, Ar-H), 8.29 (s, 1H, Ar-H), 9.22 (s, 1H, NH), 10.27 (s, 1H, NH), 13.15 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [152.42 (C), 140.44 (C), 137.76 (C), 130.56 (C–Cl), 126.66(CH), 117.65 (CH), 116.74 (CH)], 185.15 (C═S), 156.93 (N═CH), Arom-C: [154.60 (C), 130.12 (C), 128.43 (CH), 127.98 (CH), 124.34 (CH), 119.38 (CH)], 58.64 (OCH_3), 25.25 (CH_3); HRMS (*m*/*z*, ESI): M^+ 373.15, [M + 2] 375.15. Anal. Calcd. for $C_{17}H_{16}ClON_5S$ (Mol. Wt. 373. 85): C, 54.61; H, 4.31; N, 18.73. Found: C, 50.43; H, 4.29; N, 18.71%.

*2.1.4.14. (E)-2-[1-(5-Chloro-1H-benzo[d]imidazol-2-yl)ethylidene] N-(3-methoxyphenyl) hydrazine carbothioamide (**7n**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 30 min. The product was a brown solid; 70% yield; m.p. 190–192 °C; IR (cm^{-1}, KBr): 3277 (NH), 1202 (C═S), 1562 (C═N), 1610 (C═C), 1280 (C–O–C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.51 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 6.77–6.97 (m, 3H, Ar-H), 7.01–7.13 (t, 1H, J = 7.9 Hz, Ar-H), 7.21–7.50 (m, 2H, Ar-H), 7.66–7.68 (d, 1H, J = 8 Hz, Ar-H), 7.97 (s, 1H, Ar-H), 10.26 (s, 1H, NH), 11.25 (s, 1H, NH), 13.15 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [152.43 (C), 140.46 (C), 137.74 (C), 130.52 (C–Cl), 126.69(CH), 117.59 (CH), 116.76 (CH)], 185.26 (C═S), 156.98 (N═CH), Arom-C: [160.90 (C), 138.24 (C), 130.03 (CH), 120.18 (CH), 121.54 (CH), 119.35 (CH)], 58.67 (OCH_3), 25.22 (CH_3); HRMS (*m*/*z*, ESI): M^+ 373.36, [M + 2] 375.36. Anal. Calcd. for $C_{17}H_{16}ClON_5S$ (Mol. Wt. 373. 85): C, 54.61; H, 4.31; N, 18.73. Found: C, 50.43; H, 4.29; N, 18.71%.

*2.1.4.15. (E)-2-[1-(5-Chloro-1H-benzo[d]imidazol-2-yl)ethylidene] N-(benzoyl) hydrazine carbothioamide (**7o**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 35 min. The product was a brown solid; 65% yield; m.p. 203–204 °C; IR (cm^{-1}, KBr): 3136 (NH), 1224 (C═S), 1577 (C═N), 1616 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.51 (s, 3H, CH_3), 7.46 (d, 1H, J = 7.9 Hz, Ar-H), 7.52 (d, 1H, J = 8 Hz, Ar-H), 7.82–7.92 (t, 1H, J = 8 Hz, Ar-H), 8.02 (s, 1H, Ar-H), 9.89 (s, 1H, NH), 13.71 (s, 1H, NH), 13.95 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [152.35 (C), 140.54 (C), 137.64 (C), 130.48 (C–Cl), 126.55(CH), 117.49 (CH), 116.66 (CH)], 184.22 (C═S), 165.77 (C═O), 156.85 (N═CH), Arom-C: [135.23 (C), 134.84 (CH), 130.37 (CH, CH), 127.68 (CH, CH)], 25.33 (CH_3); HRMS (*m*/*z*, ESI): M^+ 371.06, [M + 2] 373.06. Anal. Calcd. for $C_{17}H_{14}ClON_5S$ (Mol. Wt. 371. 86): C, 54.91; H, 3.79; N, 18.83. Found: C, 54.37; H, 3.77; N, 18.80%.

*2.1.4.16. (E)-2-[1-(5-Chloro-1H-benzo[d]imidazol-2-yl)ethylidene] N-(4-fluorophenyl) hydrazine carbothioamide (**7p**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 30 min. The product was a brown solid; 75% yield; m.p. 195–197 °C; IR (cm^{-1}, KBr): 3246 (NH), 1217 (C═S), 1583 (C═N), 1618(C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.51 (s, 3H, CH_3), 6.54–6.83 (m, 2H, Ar-H), 7.13–7.15 (d, 1H, J = 8 Hz, Ar-H), 7.42–8.05 (m, 4H, Ar-H), 9.38 (s, 1H, NH), 10.07 (s, 1H, NH), 13.03 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [152.40 (C), 140.55 (C), 137.68 (C), 130.51 (C–Cl), 126.58 (CH), 117.52 (CH), 116.67 (CH)], 184.30 (C═S), 156.95 (N═CH), Arom-C: [165.35 (C–F), 135.18 (C), 130.27 (CH, CH), 116.68 (CH, CH)], 25.36 (CH_3); HRMS (*m*/*z*, ESI): M^+ 361.25, [M + 2] 363.25. Anal. Calcd. for $C_{16}H_{13}ClFN_5S$ (Mol. Wt. 361.82): C, 53.11; H, 3.62; N, 19.36. Found: C, 53.08; H, 3.60; N, 19.33%.

*2.1.4.17. (E)-2-[1-(5-Chloro-1H-benzo[d]imidazol-2-yl)ethylidene] N-(4-iodophenyl) hydrazine carbothioamide (**7q**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 35 min. The product was a brown solid; 78% yield; m.p. 198–199 °C; IR (cm^{-1}, KBr): 3246 (NH), 1218 (C═S), 1583 (C═N), 1616 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.51 (s, 3H, CH_3), 6.40–6.42 (d, 1H, J = 8 Hz, Ar-H), 7.15–7.27 (m, 2H, Ar-H), 7.43–7.87 (m, 2H, Ar-H), 7.95–7.98 (d, 1H, J = 7.9 Hz, Ar-H), 8.29 (s, 1H, Ar-H), 9.25 (s, 1H, NH), 11.37 (s, 1H, NH), 13.14 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [152.45 (C), 140.44 (C), 137.75 (C), 130.48 (C–Cl), 126.53 (CH), 117.57 (CH), 116.71 (CH)], 184.05 (C═S), 156.98 (N═CH), Arom-C: [139.21 (CH, CH), 138.33 (C), 127.56 (CH, CH), 95.32 (C–I)], 25.40 (CH_3); HRMS (*m*/*z*, ESI): M^+ 468.93, [M + 2] 470.93. Anal. Calcd. for $C_{16}H_{13}ClIN_5S$ (Mol. Wt. 469.73): C, 40.91; H, 2.79; N, 14.91. Found: C, 40.88; H, 2.77; N, 14.89%.

*2.1.4.18. (E)-2-[1-(5-Chloro-1H-benzo[d]imidazol-2-yl)ethylidene] N-(4-tosyl) hydrazine carbothioamide (**7r**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 30 min. The product was a brown solid; 73% yield; m.p. 190–192 °C; IR (cm^{-1}, KBr): 3240 (NH), 1218 (C═S), 1572 (C═N), 1610 (C═C); ^{1}H NMR

(400 MHz, DMSO-d_6): δ 2.38 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 7.28–7.74 (m, 6H, Ar-H) 7.98 (s, 1H, Ar-H), 8.23 (s, 1H, NH), 10.07 (s, 1H, NH), 12.23 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [152.46 (C), 140.62 (C), 137.74 (C), 130.55 (C–Cl), 126.64 (CH), 117.58 (CH), 116.70 (CH)], 184.28 (C═S), 157.15 (N═CH), Arom-C: [142.16 (C), 141.78 (C), 130.54 (CH, CH), 127.48 (CH, CH)], 35.65 (CH_3), 25.46 (CH_3); HRMS (*m*/*z*, ESI): M^+ 357.18, [M + 2] 359.18. Anal. Calcd. for $C_{17}H_{16}ClN_5S$ (Mol. Wt. 357. 86): C, 57.06; H, 4.51; N, 19.57. Found: C, 57.00; H, 4.48; N, 19.55%.

*2.1.4.19. (E)-2-[1-(5-Chloro-1H-benzo[d]imidazol-2-yl)ethylidene] N-(2,3-dichlorophenyl) hydrazine carbothioamide (**7s**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 30 min. The product was a brown solid; 68% yield; m.p. 182–184 °C; IR (cm^{-1}, KBr): 3296 (NH), 1217 (C═S), 1572 (C═N), 1583 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.51 (s, 3H, CH_3), 6.51–6.53 (d, 1H, *J* = 8 Hz, Ar-H), 7.15–7.17 (d, 1H, *J* = 7.9 Hz, Ar-H), 7.19–8.30 (m, 3H, Ar-H), 8.48 (s, 1H, Ar-H), 9.55 (s, 1H, NH), 10.41 (s, 1H, NH), 12.92 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [152.34 (C), 140.69 (C), 137.77 (C), 130.54 (C–Cl), 126.69 (CH), 117.63 (CH), 116.74 (CH)], 184.16 (C═S), 157.22 (N═CH), Arom-C: [139.03 (C), 138.36 (C–Cl), 134.54 (C–Cl), 134.50 (CH), 133.22 (CH), 130.47 (CH)], 25.55 (CH_3); HRMS (*m*/*z*, ESI): M^+ 411.92, [M + 2] 413.92. Anal. Calcd. for $C_{16}H_{12}Cl_3N_5S$ (Mol. Wt. 412.72): C, 46.56; H, 2.93; N, 16.97. Found: C, 46.54; H, 2.90; N, 16.95%.

*2.1.4.20. (E)-2-[1-(5-Chloro-1H-benzo[d]imidazol-2-yl)ethylidene] N-(3,4-dichlorophenyl) hydrazine carbothioamide (**7t**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 30 min. The product was a brown solid; 65% yield; m.p. 183–184 °C; IR (cm^{-1}, KBr): 3321 (NH), 1217 (C═S), 1581 (C═N), 1618 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.51 (s, 3H, CH_3), 7.31–7.33 (d, 1H, *J* = 7.9 Hz, Ar-H), 7.54–7.83 (m, 4H, Ar-H), 8.46 (s, 1H, Ar-H), 9.65 (s, 1H, NH), 10.02 (s, 1H, NH), 12.52 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [152.56(C), 140.75 (C), 137.80 (C), 130.55 (C–Cl), 126.71 (CH), 117.68 (CH), 116.77 (CH)], 184.32 (C═S), 157.30 (N═CH), Arom-C: [139.12 (C), 138.39 (CH), 134.58 (C–Cl), 133.42 (C–Cl), 133.12 (CH), 126.03 (CH)], 25.42 (CH_3); HRMS (*m*/*z*, ESI): M^+ 411.95, [M + 2] 413.95. Anal. Calcd. for $C_{16}H_{12}Cl_3N_5S$ (Mol. Wt. 412.72): C, 46.56; H, 2.93; N, 16.97. Found: C, 46.54; H, 2.90; N, 16.95%.

*2.1.5. General procedure illustrating the synthesis of (E)-2-[1-(1H-benzo[d]imidazol-2-yl)ethylidene] N-hydrazine carbothioamide (**8a**–**8t**)*

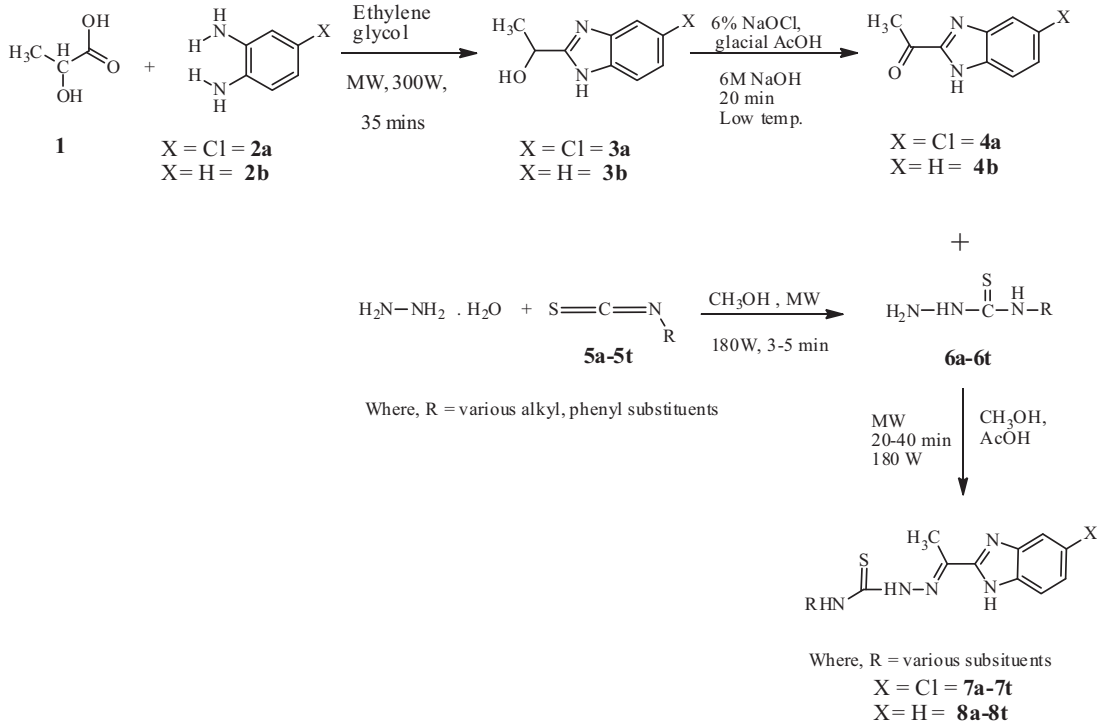
Another series of compounds (**8a**–**8t**) were also synthesized and purified similarly by the general method described in Section 2.1.4, taking compound **4b** as a starting material. (Refer Scheme 1).

*2.1.5.1. (E)-2-[1-(1H-Benzo[d]imidazol-2-yl)ethylidene]hydrazine carbothioamide (**8a**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 25 min. The product was a light brown solid; 77% yield; m.p. 216 °C; IR (cm^{-1}, KBr): 3354 (NH), 1215 (C═S), 1535 (C═N), 1596 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.48 (s, 3H, CH_3), 7.16–7.18(d, 1H, *J* = 8 Hz, Ar-H), 7.39–7.42 (d, 1H, *J* = 8.5 Hz, Ar-H), 7.77–7.95 (m, 2H, Ar-H), 8.64 (s, 2H, NH_2), 10.70 (s, 1H, NH), 12.86 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [153.24 (C), 136.25 (C, C), 128.57 (CH, CH), 118.63 (CH, CH)], 178.19 (C═S), 157.35 (N═CH), 25.24 (CH_3); HRMS (*m*/*z*, ESI): M^+ 233.03, [M + 1] 234.03. Anal. Calcd. for $C_{10}H_{11}N_5S$ (Mol. Wt. 233.29): C, 51.48; H, 4.75; N, 30.02. Found: C, 51.42; H, 4.70; N, 29.98.%.

*2.1.5.2. (E)-2-[1-(1H-Benzo[d]imidazol-2-yl)ethylidene] N-phenyl hydrazine carbothioamide (**8b**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 30 min. The product was a brown color solid in 82% yield and m.p. at 165–167 °C; IR (cm^{-1}, KBr): 3225 (NH), 1202 (C═S), 1519 (C═N), 1599 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.48 (s, 3H, CH_3), 7.27–7.29 (d, 1H, *J* = 7.9 Hz, Ar-H), 7.40–7.44 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.51–7.54 (d, 1H, *J* = 8.5 Hz, Ar-H), 7.59–7.62 (d, 1H, *J* = 8 Hz, Ar-H), 8.35–8.37 (d, 1H, *J* = 8 Hz, Ar-H), 10.38 (s, 1H, NH), 11.07 (s, 1H, NH), 13.05 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [153.28 (C), 136.30 (C, C), 128.60 (CH, CH), 118.68 (CH, CH)], 185.14 (C═S), 157.44 (N═CH), Arom-C: [140.10 (C), 132.33 (CH, CH), 130.67 (CH), 127.46 (CH)], 25.36 (CH_3); HRMS (*m*/*z*, ESI): M^+ 309.12, [M + 1] 310.13. Anal. Calcd. for $C_{16}H_{15}N_5S$ (Mol. Wt. 309.38): C, 62.11; H, 4.89; N, 22.64. Found: C, 62.08; H, 4.85; N, 22.62%.

*2.1.5.3. (E)-2-[1-(1H-Benzo[d]imidazol-2-yl)ethylidene] N-ethyl hydrazine carbothioamide (**8c**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 25 min. The product was a brown solid; 69% yield; m.p. 226–228 °C; IR (cm^{-1}, KBr): 3437 (NH), 1213 (C═S), 1525 (C═N), 1589 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.50 (s, 3H, CH_3), 1.14–1.22 (t, 3H, *J* = 8 Hz, CH_3), 3.59–3.92 (m, 2H, CH_2) 7.20–7.82 (m, 4H, Ar-H), 9.01 (s, 1H, NH), 10.68 (s, 1H, NH), 12.69 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [151.69 (C), 136.45 (C, C), 128.65 (CH, CH), 118.73 (CH, CH)], 178.31 (C═S), 157.48 (N═CH), 46.07 (CH_2), 28.49 (CH_3), 25.46 (CH_3); HRMS (*m*/*z*, ESI): M^+ 261.11, [M + 1] 262.11. Anal. Calcd. for $C_{12}H_{15}N_5S$ (Mol. Wt. 261.34): C, 55.15; H, 5.79; N, 26.80. Found: C, 55.13; H, 5.76; N, 26.78%.

*2.1.5.4. (E)-2-[1-(1H-Benzo[d]imidazol-2-yl)ethylidene] N-(n-butyl) hydrazine carbothioamide (**8d**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 25 min. The product was a brown solid; 68% yield; m.p. 210 °C; IR (cm^{-1}, KBr): 3453 (NH), 1216 (C═S), 1419 (C═N), 1541 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.26–1.97 (m, 5H, CH_3CH_2), 2.46 (s, 3H, CH_3), 4.03–4.45 (m, 2H, CH_2), 7.21–7.68 (m, 6H, Ar-H), 8.98 (s, 1H, NH), 10.65 (s, 1H, NH), 12.78 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [151.72 (C), 136.50 (C, C), 128.70 (CH, CH), 118.78 (CH, CH)], 178.71 (C═S), 157.56 (N═CH), n-butyl:[46.22 (CH_2), 35.79 (CH_2), 30.66 (CH_2), 25.39 (CH_3)], 25.43 (CH_3); HRMS (*m*/*z*, ESI): M^+ 289.14, [M + 1] 290.14. Anal. Calcd. for $C_{14}H_{19}N_5S$ (Mol. Wt. 289.39): C, 58.10; H, 6.62; N, 24.20. Found: C, 58.02; H, 6.60; N, 24.15%.



Scheme 1 Synthesis route for desired thiosemicarbazone derivatives.

*2.1.5.5. (E)-2-[1-(1H-Benzo[d]imidazol-2-yl)ethylidene] N-cyclohexyl hydrazine carbothioamide (**8e**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 25 min. The product was a brown solid; 72% yield; m.p. 214 °C; IR (cm^{-1}, KBr): 3369 (NH), 1211 (C═S), 1500 (C═N), 1581 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6):δ 1.26–1.91 (m, 11H, cyclohex), 2.50 (s, 3H, CH $_3$), 7.21–7.24 (d, 1H, J = 7.9 Hz, Ar-H), 7.51–7.54 (d, 1H, J = 8.5 Hz, Ar-H), 7.68–7.70 (d, 1H, J = 8 Hz, Ar-H), 8.58 (s, 1H, NH), 10.53 (s, 1H, NH), 12.76 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [151.74 (C), 136.54 (C, C), 128.75 (CH, CH), 118.80 (CH, CH)], 178.77 (C═S), 157.66 (N═CH), cyclohexyl C:[60.21 (C), 45.66 (CH_2,CH_2)], 36.32 (CH_2), 30.33 (CH_2, CH_2)], 25.45 (CH_3); HRMS (m/z, ESI): M^+ 315.15, [M + 1] 316.15. Anal. Calcd. for $C_{16}H_{21}N_5S$ (Mol. Wt. 315.43): C, 60.92; H, 6.71; N, 22.20. Found: C, 60.90; H, 6.68; N, 22.15.%.

*2.1.5.6. (E)-2-[1-(1H-Benzo[d]imidazol-2-yl)ethylidene] N-(4-chlorophenyl) hydrazine carbothioamide (**8f**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 30 min. The product was a brown solid; 62% yield; m.p. 175–176 °C; IR (cm^{-1}, KBr): 3458 (NH), 1201 (C═S), 1541 (C═N), 1597 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.50 (s, 3H, CH_3), 7.10–7.12 (d, 1H, J = 8 Hz, Ar-H), 7.21–7.70 (m, 6H, Ar-H), 9.24 (s, 1H, NH), 11.23 (s, 1H, NH), 13.03 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [151.72 (C), 136.59 (C, C), 128.70 (CH, CH), 118.75 (CH, CH)], 185.07 (C═S), 157.46 (N═CH), Arom-C: [140.23 (C), 135.67 (C–Cl), 130.12 (CH, CH), 128.88 (CH, CH)], 25.48 (CH_3); HRMS (m/z, ESI): M^+ 343.07, [M + 2] 345.07. Anal. Calcd. for $C_{16}H_{14}ClN_5S$ (Mol. Wt. 343.83): C, 55.89; H, 4.10; N, 20.37. Found: C, 55.85; H, 4.05; N, 20.35%.

*2.1.5.7. (E)-2-[1-(1H-Benzo[d]imidazol-2-yl)ethylidene] N-(4-nitrophenyl) hydrazine carbothioamide (**8g**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 30 min. The product was a brown solid; 60% yield; m.p. 204–206 °C; IR (cm^{-1}, KBr): 3203 (NH), 1199 (C═S), 1546 (C═N), 1595 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.56 (s, 3H, CH_3), 7.12–7.15 (d, 1H, J = 8.9 Hz, Ar-H), 7.23–7.26 (d, 1H, J = 9 Hz, Ar-H), 7.72–7.75 (d, 1H, J = 8.9 Hz, Ar-H), 7.85–7.88 (d, 1H, J = 8.9 Hz, Ar-H), 8.17–8.20 (d, 1H, J = 8 Hz, AR-H), 9.63 (s, 1H, NH), 10.67 (s, 1H, NH), 12.94 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [151.78 (C), 136.63 (C, C), 128.74 (CH, CH), 118.81 (CH, CH)], 185.16 (C═S), 157.55 (N═CH), Arom-C: [150.06 (C), 152.27 (C–NO_2), 130.22 (CH, CH), 130.58 (CH, CH)], 25.51 (CH_3); HRMS (m/z, ESI): M^+ 354.08, [M + 1] 355.08. Anal. Calcd. for $C_{16}H_{14}N_6O_2S$ (Mol. Wt. 354.38): C, 54.23; H, 3.98; N, 23.71. Found: C, 54.20; H, 3.95; N, 23.66%.

*2.1.5.8. (E)-2-[1-(1H-Benzo[d]imidazol-2-yl)ethylidene] N-(4-methoxyphenyl) hydrazine carbothioamide (**8h**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 30 min. The product was a brown solid; 78% yield; m.p. 196–198 °C; IR (cm^{-1}, KBr): 3444 (NH), 1202 (C═S), 1539 (C═N), 1602 (C═C), 1249 (C–O–C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.51 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 6.51–6.55 (d, 1H, J = 9.5 Hz, Ar-H), 7.01–7.05 (d, 1H, J = 9.5 Hz, Ar-H), 7.20–7.24 (d, 1H, J = 9.5 Hz, Ar-H), 7.66–7.68 (d, 1H, J = 8 Hz, Ar-H), 8.62–8.84 (d, 1H, J = 8 Hz, Ar-H), 10.38 (s, 1H, NH), 11.01 (s, 1H, NH), 12.87 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [151.75 (C), 136.65 (C, C), 128.76 (CH, CH), 118.75 (CH, CH)], 185.34 (C═S), 157.59 (N═CH), Arom-C:

[162.45 (C–OCH_3), 142.37 (C), 130.28 (CH, CH), 120.08 (CH, CH)], 58.50 (OCH_3), 25.54 (CH_3); HRMS (*m/z*, ESI): M^+ 339.12, [M + 1] 340.12. Anal. Calcd. for $C_{17}H_{17}ON_5S$ (Mol. Wt. 339.39): C, 60.16; H, 5.05; N, 20.63. Found: C, 60.10; H, 4.98; N, 20.60%.

*2.1.5.9. (E)-2-[1-(1H-Benzo[d]imidazol-2-yl)ethylidene] N-(isopropyl) hydrazine carbothioamide (**8i**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 25 min. The product was a brown solid; 75% yield; m.p. 224–226 °C; IR (cm^{-1}, KBr): 3448 (NH), 2978($C(CH_3)$), 1211 (C═S), 1498 (C═N), 1530 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30–1.33 (d, 6H, *J* = 9.5 Hz, (CH_3)$_2$), 2.50 (s, 3H, CH_3), 4.36–4.64 (m, 1H, CH), 7.12–7.69 (m, 4H, Ar-H), 8.61 (s, 1H, NH), 10.68 (s, 1H, NH), 12.78 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [151.77 (C), 136.62 (C, C), 128.72 (CH, CH), 118.78 (CH, CH)], 179.33 (C═S), 157.60 (N═CH), iso-propyl-C:[58.67 (CH), 36.56 (CH_3,CH_3)], 25.56 (CH_3); HRMS (*m/z*, ESI): M^+ 275.10, [M + 1] 276.10. Anal. Calcd. for $C_{13}H_{17}N_5S$ (Mol. Wt. 275.37): C, 56.70; H, 6.22; N, 25.43. Found: C, 56.67; H, 6.19; N, 25.40%.

*2.1.5.10. (E)-2-[1-(1H-Benzo[d]imidazol-2-yl)ethylidene] N-(tert-butyl) hydrazine carbothioamide (**8j**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 25 min. The product was a brown solid; 72% yield; m.p. 220–222 °C; IR (cm^{-1}, KBr): 3381 (NH), 1230 (C═S), 1514 (C═N), 1560 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.37–1.71 (m, 9H, $(CH_3)_3$), 2.50 (s, 3H, CH_3), 7.12–7.98 (m, 8H, Ar-H), 8.45–8.48 (d, 1H, *J* = 8.5 Hz, Ar-H), 10.28 (s, 1H, NH), 12.82 (s, 1H, NH), 13.78 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [151.67 (C), 136.60 (C, C), 128.68 (CH, CH), 118.73 (CH, CH)], 179.27 (C═S), 157.55 (N═CH), t-butyl-C:[65.20 (C), 32.48 (CH_3,CH_3,CH_3)], 25.52 (CH_3); HRMS (*m/z*, ESI): M^+ 289.14, [M + 1] 290.14. Anal. Calcd. for $C_{14}H_{19}N_5S$ (Mol. Wt. 289.39): C, 58.10; H, 6.62; N, 24.20. Found: C, 58.05; H, 6.60; N, 24.18%.

*2.1.5.11. (E)-2-[1-(1H-Benzo[d]imidazol-2-yl)ethylidene] N-(benzyl) hydrazine carbothioamide (**8k**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 35 min. The product was a brown solid; 60% yield; m.p. 219–220 °C; IR (cm^{-1}, KBr): 3383 (NH), 1211 (C═S), 1523 (C═N), 1573 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.50 (s, 3H, CH_3), 4.28–4.45 (m, 2H, CH_2), 7.21–7.69 (m, 4H, Ar-H), 8.43–8.58 (d, 1H, *J* = 9.5 Hz, Ar-H), 9.05 (s, 1H, NH), 10.53 (s, 1H, NH), 12.77 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [151.68 (C), 136.66 (C, C), 128.70 (CH, CH), 118.75 (CH, CH)], 183.30 (C═S), 157.58 (N═CH), Arom-C: [142.35 (C), 132.38 (CH, CH), 131.65 (CH, CH), 130.85 (CH)], 55.08 (CH_2), 25.32 (CH_3); HRMS (*m/z*, ESI): M^+ 323.12, [M + 1] 324.12. Anal. Calcd. for $C_{17}H_{17}N_5S$ (Mol. Wt. 323.41): C, 63.13; H, 5.30; N, 21.65. Found: C, 63.10; H, 5.25; N, 21.62%.

*2.1.5.12. (E)-2-[1-(1H-Benzo[d]imidazol-2-yl)ethylidene] N-(2,4-dichlorophenyl) hydrazine carbothioamide (**8l**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 35 min. The product was a brown solid; 68% yield; m.p. 185–187 °C; IR (cm^{-1}, KBr): 3389 (NH), 1240 (C═S), 1545 (C═N), 1583 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6):δ 2.50 (s, 3H, CH_3), 7.28–7.81 (m, 5H, Ar-H), 8.39 (d, 1H, Ar-H), 9.55 (s, 1H, Ar-H), 10.39 (s, 1H, NH), 11.39 (s, 1H, NH), 12.77 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [151.62 (C), 136.56 (C, C), 128.72 (CH, CH), 118.77 (CH, CH)], 185.40 (C═S), 157.68 (N═CH), Arom-C: [138.15 (C), 137.43 (C–Cl), 136.85 (CH), 135.65 (C–Cl), 134.88 (CH), 126.25 (CH)], 25.44 (CH_3); HRMS (*m/z*, ESI): M^+ 377.57, [M + 2] 379.57. Anal. Calcd. for $C_{16}H_{13}Cl_2N_5S$ (Mol. Wt. 378.27): C, 50.80; H, 3.46; N, 18.51. Found: C, 50.75; H, 3.43; N, 18.45%.

*2.1.5.13. (E)-2-[1-(1H-Benzo[d]imidazol-2-yl)ethylidene] N-(2-methoxyphenyl) hydrazine carbothioamide (**8m**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 30 min. The product was a brown solid; 65% yield; m.p. 194–196 °C; IR (cm^{-1}, KBr): 3296 (NH), 1242 (C═S), 1575 (C═N), 1599 (C═C), 1275 (C–O–C); ^{1}H NMR (400 MHz, DMSO-d_6):δ 2.50 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 6.63–7.65 (d, 1H, *J* = 8 Hz, Ar-H), 7.13–7.89 (m, 1H, Ar-H), 7.93–7.95 (d, 1H, *J* = 7.9 Hz, Ar-H), 7.95–7.99 (t, 1H, *J* = 7.9 Hz, Ar-H), 8.02–8.06 (d, 1H, *J* = 8 Hz, Ar-H), 8.13–8.32 (d, 1H, *J* = 8.5 Hz, Ar-H), 8.53–8.76 (d, 1H, *J* = 8.2 Hz, Ar-H), 9.84 (s, 1H, NH), 10.47 (s, 1H, NH), 12.83 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [151.65 (C), 136.52 (C, C), 128.77 (CH, CH), 118.79 (CH, CH)], 185.57 (C═S), 157.71 (N═CH), Arom-C: [160.44 (C–OCH_3), 135.13 (CH), 134.84 (C), 134.18 (CH), 130.56 (CH), 120.24 (CH)], 62.45 (OCH_3), 25.56 (CH_3); HRMS (*m/z*, ESI): M^+ 339.16, [M + 1] 340.16. Anal. Calcd. for $C_{17}H_{17}ON_5S$ (Mol. Wt. 339.41): C, 60.16; H, 5.05; N, 20.63. Found: C, 60.14; H, 5.00; N, 20.60%.

*2.1.5.14. (E)-2-[1-(1H-Benzo[d]imidazol-2-yl)ethylidene] N-(3-methoxyphenyl) hydrazine carbothioamide (**8n**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 30 min. The product was a brown solid; 69% yield; m.p. 194–196 °C; IR (cm^{-1}, KBr): 3273 (NH), 1195 (C═S), 1576 (C═N), 1598 (C═C), 1280 (C–O–C); ^{1}H NMR (400 MHz, DMSO-d_6):δ 2.50 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 6.66 (d, 1H, *J* = 7.9 Hz, Ar-H), 6.88 (d, 1H, *J* = 8.5 Hz, Ar-H), 7.13–7.70 (m, 6H, Ar-H), 9.17 (s, 1H, NH), 10.42 (s, 1H, NH), 11.08 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [151.45 (C), 136.48 (C, C), 128.72 (CH, CH), 118.74 (CH, CH)], 185.53 (C═S), 157.65 (N═CH), Arom-C: [163.58 (C–OCH_3), 140.22 (C), 132.68 (CH), 120.13 (CH), 118.55 (CH), 116.45 (CH)], 65.20 (OCH_3), 25.36 (CH_3); HRMS (*m/z*, ESI): M^+ 339.09, [M + 1] 340.09. Anal. Calcd. for $C_{17}H_{17}ON_5S$ (Mol. Wt. 339.41): C, 60.16; H, 5.05; N, 20.63. Found: C, 60.14; H, 5.00; N, 20.60%.

*2.1.5.15. (E)-2-[1-(1H-Benzo[d]imidazol-2-yl)ethylidene] N-(benzoyl) hydrazine carbothioamide (**8o**).* The reaction mass was heated in MW at 180 W with a total irradiation time of 35 min. The product was a brown solid; 60% yield; m.p. 205–207 °C; IR (cm^{-1}, KBr): 3145 (NH), 1228 (C═S), 1580 (C═N), 1612 (C═C), 1725(C═O); ^{1}H NMR (400 MHz, DMSO-d_6):δ 2.51 (s, 3H, CH_3), 7.14–7.92 (m, 5H, Ar-H), 8.02 (d, 1H, *J* = 8 Hz, Ar-H), 9.87 (s, 1H, NH), 13.74 (s, 1H, NH), 13.86 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [151.48 (C), 136.52 (C, C), 128.75 (CH, CH), 118.78 (CH, CH)], 185.44 (C═S), 172.45 (C═O),

157.62 (N═CH), Arom-C: [139.33 (C), 138.11 (CH), 132.65 (CH, CH), 131.83 (CH, CH)], 25.46 (CH_3); HRMS (*m*/*z*, ESI): M^+ 337.14, [M + 1] 338.14. Anal. Calcd. for $C_{17}H_{15}ON_5S$ (Mol. Wt. 337.39): C, 60.52; H, 4.48; N, 20.76. Found: C, 60.49; H, 4.45; N, 20.73%.

*2.1.5.16. (E)-2-[1-(1H-Benzo[d]imidazol-2-yl)ethylidene] N-(4-fluorophenyl) hydrazine carbothioamide (**8p**)*. The reaction mass was heated in MW at 180 W with a total irradiation time of 35 min. The product was a brown solid; 73% yield; m.p. 198–199 °C; IR (cm^{-1}, KBr): 3313 (NH), 1213 (C═S), 1548 (C═N), 1583 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6):δ 2.51 (s, 3H, CH_3), 6.68 (d, 1H, *J* = 7.5 Hz, Ar-H), 7.12 (d, 1H, *J* = 8 Hz, Ar-H), 7.46–7.98 (m, 4H, Ar-H), 9.16 (s, 1H, NH), 10.25 (s, 1H, NH), 13.03 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [151.52 (C), 136.60 (C, C), 128.80 (CH, CH), 118.82 (CH, CH)], 185.53 (C═S), 157.65 (N═CH), Arom-C: [166.23 (C–F), 138.33 (C), 132.12 (CH, CH), 118.89 (CH, CH)], 25.56 (CH_3); HRMS (*m*/*z*, ESI): M^+ 327.10, [M + 1] 328.10. Anal. Calcd. for $C_{16}H_{14}FN_5S$ (Mol. Wt. 327.37): C, 58.70; H, 4.31; N, 21.39. Found: C, 58.65; H, 4.27; N, 21.36%.

*2.1.5.17. (E)-2-[1-(1H-Benzo[d]imidazol-2-yl)ethylidene] N-(4-iodophenyl) hydrazine carbothioamide (**8q**)*. The reaction mass was heated in MW at 180 W with a total irradiation time of 35 min. The product was a brown solid; 75% yield; m.p. 197–199 °C; IR(cm^{-1}, KBr): 3294 (NH), 1202 (C═S), 1548 (C═N), 1596 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6):δ 2.50 (s, 3H, CH_3), 6.41–6.44 (d, 1H, *J* = 9 Hz, Ar-H), 7.12–7.80 (m, 5H, Ar-H), 9.25 (s, 1H, NH), 10.43 (s, 1H, NH), 12.94 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [151.45 (C), 136.67 (C, C), 128.82 (CH, CH), 118.85 (CH, CH)], 185.48 (C═S), 157.63 (N═CH), Arom-C: [143.22 (CH, CH), 142.97 (C), 134.49 (CH, CH), 95.77 (C–I)], 25.67 (CH_3); HRMS (*m*/*z*, ESI): M^+ 435.02, [M + 1] 436.02. Anal. Calcd. for $C_{16}H_{14}IN_5S$ (Mol. Wt. 435.28): C, 44.15; H, 3.24; N, 16.09. Found: C, 44.10; H, 3.22; N, 16.02%.

*2.1.5.18. (E)-2-[1-(1H-Benzo[d]imidazol-2-yl)ethylidene] N-(4-tosyl) hydrazine carbothioamide (**8r**)*. The reaction mass was heated in MW at 180 W with a total irradiation time of 30 min. The product was a brown solid; 70% yield; m.p. 195–197 °C; IR (cm^{-1}, KBr): 3298 (NH), 1234 (C═S), 1548 (C═N), 1585 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6):δ 2.37 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 7.10–7.48 (m, 1H, Ar-H), 7.68–7.72 (d, 1H, *J* = 9 Hz, Ar-H), 7.79 (d, 1H, *J* = 7.9 Hz, Ar-H), 7.89 (d, 1H, *J* = 7.9 Hz, Ar-H), 9.12 (s, 1H, NH), 10.15 (s, 1H, NH), 12.34 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [151.48 (C), 136.68 (C, C), 128.78 (CH, CH), 118.82 (CH, CH)], 185.54 (C═S), 157.62 (N═CH), Arom-C: [142.32 (C–CH_3), 135.67 (C), 130.56 (CH, CH), 126.47 (CH, CH)], 32.46 (CH_3), 25.67 (CH_3); HRMS (*m*/*z*, ESI): M^+ 323.06, [M + 1] 324.06. Anal. Calcd. for $C_{17}H_{17}N_5S$ (Mol. Wt. 323.41): C, 63.13; H, 5.30; N, 21.65. Found: C, 63.10; H, 5.25; N, 21.63%.

*2.1.5.19. (E)-2-[1-(1H-Benzo[d]imidazol-2-yl)ethylidene] N-(2,3-dichlorophenyl) hydrazine carbothioamide (**8s**)*. The reaction mass was heated in MW at 180 W with a total irradiation time of 35 min. The product was a brown solid; 66% yield; m.p. 185–187 °C; IR (cm^{-1}, KBr): 3246 (NH), 1180 (C═S), 1533 (C═N), 1594 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6):δ 2.5 (s, 3H, CH_3), 7.12 (d, 1H, *J* = 8.9 Hz, Ar-H), 7.35 (d, 1H, *J* = 9.5 Hz, Ar-H), 7.43 (d, 1H, *J* = 9 Hz, Ar-H), 8.27 (d, 1H, *J* = 8.9 Hz, Ar-H), 9.70 (s, 1H, NH), 10.38 (s, 1H, NH), 12.92 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [151.52 (C), 136.70 (C, C), 128.76 (CH, CH), 118.81 (CH, CH)], 185.59 (C═S), 157.66 (N═CH), Arom-C: [142.18 (C), 141.35 (C–Cl), 140.73 (C–Cl), 139.97 (CH), 135.05 (CH), 130.28 (CH)], 25.66 (CH_3); HRMS (*m*/*z*, ESI): M^+ 377.37, [M + 2] 379.38. Anal. Calcd. for $C_{16}H_{13}Cl_2N_5S$ (Mol. Wt. 378.27): C, 50.80; H, 3.46; N, 18.51. Found: C, 50.75; H, 3.43; N, 18.47%.

*2.1.5.20. (E)-2-[1-(1H-Benzo[d]imidazol-2-yl)ethylidene] N-(3,4-dichlorophenyl) hydrazine carbothioamide (**8t**)*. The reaction mass was heated in MW at 180 W with a total irradiation time of 35 min. The product was a brown solid; 68% yield; m.p. 186–188 °C; IR (cm^{-1}, KBr): 3296 (NH), 1213 (C═S), 1566 (C═N), 1598 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6):δ 2.50 (s, 3H, CH_3), 6.52–6.54 (d, 1H, *J* = 8 Hz, Ar-H), 6.84 (d, 1H, *J* = 8 Hz, Ar-H), 7.17–7.98 (m, 4H, Ar-H), 8.07–8.10 (d, 1H, *J* = 8.5 Hz, Ar-H), 9.40 (s, 1H, NH), 10.04 (s, 1H, NH), 12.56 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ Benzimidazole C: [151.57 (C), 136.74 (C, C), 128.79 (CH, CH), 118.77 (CH, CH)], 185.62 (C═S), 157.68 (N═CH), Arom-C: [140.35 (C), 139.69 (CH), 135.85 (C–Cl), 135.25 (C–Cl), 135.08 (CH), 125.18 (CH)], 25.58 (CH_3); HRMS (*m*/*z*, ESI): M^+ 377.45, [M + 2] 379.47. Anal. Calcd. for $C_{16}H_{13}Cl_2N_5S$ (Mol. Wt. 378.27): C, 50.80; H, 3.46; N, 18.51. Found: C, 50.75; H, 3.43; N, 18.47%.

2.2. Anti-malarial activity

2.2.1. Sample preparation

A stock solution of 5 mg/mL of each of the test samples as well as standards was prepared in DMSO and subsequent dilutions were prepared with the culture medium. The diluted samples in 20 µl volume were added to the test wells so as to obtain final concentrations (at five fold dilutions) ranging between 0.4 and 100 µg/mL in duplicate well containing parasitized cell preparation.

2.2.2. Assay for in vitro antimalarial activity

The *in vitro* antimalarial assay was carried out in 96 well microtitre plates according to the microassay protocol of Reickmann and co-workers (1978) with minor modifications. The cultures of *P. falciparum* strain were maintained in medium RPMI 1640 supplemented with 25 mM HEPES, 1% D-glucose, 0.23% sodium bicarbonate and 10% heat inactivated human serum. The asynchronous parasites of *P. falciparum* were synchronized after 5% D-sorbitol treatment to obtain only the ring stage parasitized cells. For carrying out the assay, an initial ring stage parasitaemia of 0.8–1.5% at 3% haematocrit in a total volume of 200 µl of medium RPMI-1640 was determined by Jaswant Singh Bhattacharya (JSB) staining (Singh, 1956) to assess the percent parasitaemia (rings) and uniformly maintained with 50% RBCs (O^{+ve}). The culture plates were incubated at 37 °C in a candle jar. After 36–40 h incubation, thin blood smears from each well were prepared

Table 1 List of thiosemicarbazone derivatives with structural variation and their IC_{50} values.

Entry	X	R	Product	IC_{50} (μg/mL)	Entry	X	R	Product	IC_{50} (μg/mL)
1	Cl	H	**7a***	0.095	21	H	H	**8a**	0.088
2	Cl	Ph	**7b***	0.87	22	H	Ph	**8b**	0.83
3	Cl	Et	**7c***	0.72	23	H	Et	**8c**	0.65
4	Cl	n-But	**7d***	0.75	24	H	n-But	**8d**	0.72
5	Cl	C_6H_{11}	**7e***	0.047	25	H	C_6H_{11}	**8e**	0.056
6	Cl	4-ClC_6H_4	**7f**	0.26	26	H	4-ClC_6H_4	**8f**	1.56
7	Cl	4-$(O_2N)C_6H_4$	**7g**	0.098	27	H	4-$(O_2N)C_6H_4$	**8g**	0.42
8	Cl	4-$MeOC_6H_4$	**7h**	0.15	28	H	4-$MeOC_6H_4$	**8h**	0.073
9	Cl	iso-Pr	**7i**	0.42	29	H	iso-Pr	**8i**	0.057
10	Cl	tert-But	**7j**	0.98	30	H	tert-But	**8j**	1.12
11	Cl	$CH_2C_6H_5$	**7k**	0.093	31	H	$CH_2C_6H_5$	**8k**	0.97
12	Cl	2,4-ClC_6H_3	**7l**	0.68	32	H	2,4-ClC_6H_3	**8l**	1.47
13	Cl	2-$MeOC_6H_4$	**7m**	1.33	33	H	2-$MeOC_6H_4$	**8m**	0.54
14	Cl	3-$MeOC_6H_4$	**7n**	1.89	34	H	3-$MeOC_6H_4$	**8n**	0.096
15	Cl	COC_6H_5	**7o**	0.023	35	H	COC_6H_5	**8o**	0.93
16	Cl	4-FC_6H_4	**7p**	0.003	36	H	4-FC_6H_4	**8p**	0.64
17	Cl	4-IC_6H_4	**7q**	0.012	37	H	4-IC_6H_4	**8q**	1.47
18	Cl	4-MeC_6H_4	**7r**	0.025	38	H	4-MeC_6H_4	**8r**	1.33
19	Cl	2.3-ClC_6H_3	**7s**	0.005	39	H	2.3-ClC_6H_3	**8s**	0.90
20	Cl	3,4-ClC_6H_3	**7t**	0.56	40	H	3,4-ClC_6H_3	**8t**	0.45

* Already reported compounds by Patel et al. (2013). Standards taken for antimalarial activity: chloroquine (0.020 μg/mL) and quinine (0.268 μg/mL).

and stained with JSB stain. The slides were microscopically observed to record maturation of the ring stage parasites into trophozoites and schizonts in the presence of different concentrations of the test agents. The test concentration which inhibited the complete maturation into schizonts was recorded as the minimum inhibitory concentration (MIC). Chloroquine and Quinine were used as the reference drugs.

3. Results and discussion

In the present work, thiosemicarbazone derivatives containing the benzimidazole moiety were prepared according to reaction as in Scheme 1. The condensation reaction between commercially available substituted benzene-1,2-diamine (**2a**–**2b**) with lactic acid (**1**) gives 1-(substituted-1*H*-benzimidazol-yl) ethanol (**3a**–**3b**) (refer Scheme 1) in quantitative yield. Originally, this reaction was performed conventionally for 4 h in a nitrogen environment at 140–150 °C (Mylonas and Mamalis, 2005). Patel et al. (2013) had developed this reaction in microwave where they gave microwave irradiation at 140 °C (300 W). Due to this compounds (**3a**–**3b**) were synthesized in 35 min only without any by-products. An introduction of ethylene glycol in reaction mass was justified for the temperature enhancement (because of its high dielectric constant of 38.66) during the reaction so that reaction could reach its optimum temperature within the short period of time. The IR spectra of compounds (**3a**–**3b**) showed sharp absorption bands, appearing between 3350 and 3430 cm^{-1}, was attributed to the NH function of compounds and other, observed between 1111 and 1130 cm^{-1}, was assigned to C–O stretching frequency. The ^1H NMR spectrum of compounds (**3a**–**3b**) exhibited two different signals between 5.60 and 5.80 ppm (OH) and near 13.0 ppm (NH), respectively. The signals of aromatic proton of compound were observed between 7.14 and 8.54 ppm.

Further oxidation of the *sec*-alcohol (**3a**–**3b**) gave the corresponding ketone (**4a**–**4b**) (refer Scheme 1). Here, we used bleach, which is a cheap, nontoxic reagent whose active component sodium hypochlorite (NaOCl) is an excellent oxidizing agent, instead of original reagent chromium trioxide (CrO_3). In earlier reported method (Patel et al., 2013) the product loss was occurring due to the usage of CrO_3 which has overcome by using NaOCl as an oxidizing agent in mild acidic condition also the previous harmful waste product has been taken care by this change. The spectral data of **4a**–**4b** showed IR band near 1670 cm^{-1} confirming the formation of ketone (C═O). Further, ^1H NMR of compounds **4a**–**4b** shown the presence of a singlet between 13.0 and 13.25 ppm indicating the amino group present (NH), 7.28–8.50 ppm shown the presence of aromatic protons.

The N^4-monosubstituted thiosemicarbazides (**6a**–**6t**) were synthesized as outlined in Scheme 1. Previously, these compounds were synthesized conventionally at room temperature (Mylonas and Mamalis, 2005; Patel et al.). We have performed this reaction under microwave irradiation which was more rapid and gave ample amount of pure product. Thiosemicarbazides were formed from hydrazine and various isothiocyanates (**5a**–**5t**) which were commercially available in the market (Mylonas and Mamalis, 2005). Patel et al. (2013) have already synthesized **7a**–**7e** by simple condensation reaction between compound **4a** and different thiosemicarbazides (**6a**–**6e**). The time for this conventional condensation was approx. 4 h. In this present work the method is modified by usage of microwave irradiation to increase the rate of reaction. A series of final compounds **7a**–**7t** were synthesized by condensation reaction between compound **4a** and **6a**–**6t**, while **8a**–**8t** were synthesized by condensation reaction between compound **4b** and **6a**–**6t**. The product obtained from the reaction was at its best purity without any by-products. Title compounds **7a**–**7t** and **8a**–**8t** showed IR bands at 3250–3460 cm^{-1} which confirmed the formation of the benzimidazole ring which was further substantiated with the help of ^1H NMR data with the peaks at 12.50–13.30 ppm and 9.20–10.98 ppm for the protons of the amino group. Peaks between 7.05 and 8.70 ppm

were observed for respective aromatic protons. Synthesis of final compounds was also confirmed by ^{13}C NMR data, peaks between 179 and 186 ppm have confirmed the formation of C═S. Peaks between 115–165 and 25.20–25.65 ppm confirmed the presence of aromatic carbons and methyl carbon, respectively. Title compounds were further confirmed by mass spectral data and elemental analysis.

The synthesized compounds **7a**–**7t** and **8a**–**8t** were screened for their *in vitro* antimalarial activity against *P. falciparum* by measuring the minimum inhibitory concentration (μg/mL) as shown in Table 1, respectively. Compounds **7o** (0.023 μg/mL), **7p** (0.003 μg/mL), **7q** (0.012 μg/mL), **7r** (0.025 μg/mL) and **7s** (0.005 μg/mL) against standard Chloroquine (0.020 μg/mL) showed excellent activity. Compounds **7a** (0.095 μg/mL), **7e** (0.047 μg/mL), **7g** (0.098 μg/mL), **7k** (0.093 μg/mL), **8a** (0.088 μg/mL), **8e** (0.053 μg/mL), **8h** (0.073 μg/mL), **8i** (0.057 μg/mL) and **8n** (0.096 μg/mL) showed moderate activity against Chloroquine (0.020 μg/mL). Compounds **7f** (0.26 μg/mL) and **7h** (0.15 μg/mL) against standard quinine (0.268 μg/mL) showed excellent activity, while remaining compounds showed moderate to very less activity against quinine (0.268 μg/mL). As structure activity relationship (SAR) study of all compounds was taken into account, it was observed that compounds having electron withdrawing functional groups like *chloro, fluoro* and *iodo* showed excellent activity. Compounds containing moderate electron releasing groups like *substituted methoxy* exhibited good antimalarial potency. The presence of some other groups like *cyclohexyl* and *isopropyl* seems to be important for the antimalarial activity.

4. Conclusion

We have demonstrated that the thiosemicarbazone derivatives **7a**–**7t** and **8a**–**8t** can be synthesized by making modifications in the reported method. The production was successful with less time duration and improved quality and quantity than the old method. Environmental issues are also resolved because of the use of the microwave and the green oxidizing agent NaOCl (Bleach) in the method. A common parameter was observed between all active compounds that they all contained electron withdrawing functional groups in their moiety. Among the compounds tested **7o**, **7p**, **7q**, **7r**, **7s**, **8a**, **8e**, **8i**, **8n** and **8h** exhibited good antimalarial activity *in vitro*. Finally, it is conceivable that further derivatization of such compounds with high and moderate electron withdrawing functional groups will be of interest with good hope to get more selective antimalarial agents.

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